The Relationship between Prognostic Factors and Overall Survival in Small Cell Lung Cancer Patients: a Single Centre Experience

Küçük Hücreli Akciğer Kanserli Olgularımızda Sağkalım ve Prognostik Faktörlerin Değerlendirilmesi: Tek Merkez Deneyimi

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ABSTRACT

Objective: Age, sex, weight loss, lactate dehydrogenase (LDH) level, hemoglobin concentration, stage and ECOG performance status (PS) have been accepted as prognostic factors for patients with small cell lung cancer (SCLC). In our study, we aim to evaluate the relationship between prognostic factors and survival in patients with SCLC.

Material and Method: A total of 106 patients with SCLC, between 2005 and 2008, were retrospectively analyzed.

Results: The median age of patients at diagnosis was 59.3 and 89.6% of patients were male; 33.1% of patients were older than 65 years and 73 patients were younger than 65 years of age. 54 out of 106 patients had limited stage disease (LSD) (52.9%), and 48 had extended stage disease (ESD) (47.1%). The ratio of PS 0-1 and 2 patients were 77.3% and 22.7% respectively. 36% of them had high serum LDH level and 29.3% had low hemoglobin level. In our study, clinical response was achieved in 71.2% of patients. Overall median survival was 14.2 months. While median survival was 19.7 month in LSD, in ESD it was 9.1 months and stage was found to be prognostic factor in multivariate analysis (p=0.001). Multivariate analysis showed that there were no correlations among median survival and PS, LDH level, weight loss, sex, age (p>0.05).

Conclusion: Although we found no relationship between prognostic factors and median survival and progression free survival, the patients with LSD had more prolonged OS than ESD. Whenever possible, more SCLC patients may be included in future clinical trials to detect the relationship between prognostic factors and overall survival time. *(Tur Toraks Der 2012; 13: 60-4)*

Key words: Small cell lung cancer, overall survival, prognosis

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ÖZET

Amaç: Akciğer kanserleri kansere bağlı ölüm nedenleri arasında ilk sırada yer almaktadır. Küçük hücreli akciğer kanserleri (KHAK) daha kötü prognoz ve daha az sağ kalım oranlarına sahip olması, tedavisinde kemoterapinin daha fazla yer alması nedeniyle, ayrı bir yere sahiptir. KHAK'de yaş, cinsiyet, kilo kaybı, LDH düzeyi, hemoglobin düzeyi, hastalığın evresi, performans durumu prognozu etkileyen faktörler arasında sayılmaktadır. Biz de bu prognostik faktörleri ve toplam sağkalımı belirlemek amacıyla 106 KHAK hastasını değerlendirdik.

Gereç ve Yöntem: Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi Tıbbi Onkoloji Kliniği'nde 2005-2008 yılları arasında takip edilen 106 KHAK vakasını retrospektif olarak değerlendirdik.

Bulgular: Yüzaltı vakanın 54'ü sınırlı evre (%52.9), 48'i yaygın evre (%47.1) hastalık idi. Median yaş 59.3 (41-88) iken 33 hasta 65 yaşının üstü, 73 hasta 65 yaş altında idi. Erkek hastalar %89.6 ile çoğunluktaydı. Hastalarımızda en sık kullandığımız tanı yöntemi bronkoskopi (%74.8) olup median 6 kür uyguladığımız en sık kemoterapi rejimi %87.8 ile cisplatin etoposid kombinasyonuydu. Tedavi sonrası %71.2 hastada cevap alındı. Ortanca sağkalım ile performans statüsü, LDH düzeyi, kilo kaybı, cinsiyet, yaş arasında multivarite analizinde istatistiksel anlamlı farklılık saptanmadı. Sınırlı evrede median sağkalım 19.7 ay iken, yaygın evre hastalıkta 9.1 ay olup istatistiksel olarak anlamlıydı (p=0.001).

Sonuç: Çalışmamızda prognostik faktörlerle genel sağkalım ve progresyonsuz sağkalım arasında ilişki bulamadık. Prognostik faktörleri değerlendirmek için artırılmış hasta sayısı ile yeni çalışmalara ihtiyaç vardır. *(Tur Toraks Der 2012; 13: 60-4)*

Anahtar sözcükler: Küçük hücreli akciğer kanseri, sağkalım, prognoz

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INTRODUCTION

Small cell lung cancer (SCLC) accounts for approximately 13-20% of bronchogenic carcinomas [1,2]. History of cigarette smoking is detected in 95% of SCLC [3]. Most cases are diagnosed in patients aged ≥65 years and age has prognostic significance in SCLC [4]. Although it was identified that female sex, ECOG performance status (PS) and LDH level were important prognostic factors in SCLC, survival strongly correlated with stage and treatment received [4,5]. Without treatment, median survival after diagnosis is 1 to 3 months. However, with combination chemotherapy, it is found as 14 to 16 months for limited stage disease (LSD) and 8 to 11 months for extensive stage disease (ESD) [2,3,6]. It is an aggressive tumor that often metastasizes before the primary cancer is diagnosed [7].

Surgery has a limited role in primary therapy. On the other hand, SCLC is sensitive to chemotherapy and radiotherapy with response rates of greater than 80% in both LSD and ESD, but complete cure is difficult to achieve [3,8]. The combination of platinum and etoposide is the accepted standard chemotherapeutic regimen. In addition, thoracic concomitant chemoradiotherapy in LSD is also applied [8]. SCLC usually recurs within one year after treatment [7]. In this study, SCLC patients treated and followed-up in the Department of Medical Oncology were retrospectively analyzed. Furthermore, we also evaluated median survival both in LSD and ESD patients and the relationship between median survival and prognostic factors in patients with SCLC.

MATERIAL and METHOD

A total of 106 patients with SCLC followed up from 2005 to 2008 in Dr. Lutfi Kirdar Education and Research Hospital, Department of Medical Oncology were included in this study. Most of the patients were diagnosed with fiberoptic bronchoscopy (74.8%) (other diagnostic tools were mediastinoscopy (7%), transthoracic fine niddle aspiration biopsy (5%), operation (5%), cytology of pleural effusion and liver biopsy). After taking the history and physical examination, patients were grouped according to ECOG PS and underwent chest-X ray and CT of the thorax. Complete blood count, biochemical tests including liver functions tests, LDH, urea and creatinine levels were measured. Based on staging, patients were classified as LSD or ESD. After the end of the second or third and fourth or sixth cycles of chemotherapy regimens, patients were reevaluated by physical examination, complete blood count, biochemical tests and radiological imaging and patients were followed-up every 3 months.

Statistical Methods

Statistical analyses were performed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA) software. Survival analysis and curves were established according to the Kaplan-Meier method and compared using the log-rank test. Progression free survival (PFS) was defined as the time from the diagnosis to the last follow-up and the time until relapse. In addition, overall survival (OS) was described as the time from diagnosis to the date of the patient's death or last known contact. Prognostic factors analyzed by univariate analysis were also evaluated with multivariate analysis using the Cox proportional hazards model to predict the risk factors for relapse and survival. Multivariate p values were used to characterize the independence of these factors. A 95% confidence interval (CI) was used to quantify the relationship between survival time and each independent factor. All p values were two-sided in tests and p values less than or equal to 0.05 were considered significant.

RESULTS

Patient characteristics including sex, age, PS, stage, weight loss, history of smoking are summarized in Table 1. The median age of patients at time of diagnosis was 59.3 (41-88). Thirty-three of them (31.1%) were older than 65 years and 73 of them (68.9%) were younger than 65 years. Ninety-five out of 106 patients were male (89.6%), 68 patients had PS of 0-1 (77.3%) at the time of diagnosis and 20 patients had PS≥2 (22.7%), 36% of patients had above the upper limit of LDH level and 29.3% had lower hemoglobin level.

During the follow-up time, 79.5% of patients lost weight. There were 54 patients with LSD (52.9%), and 48 with ESD (47.1%). The majority of patients (87.8%)

Table 1. The characteristics of 106 patients with small cell lung cancer

	n	%
Age, median (range)	59.3 (41-88)	
>65 years	33 (41-88)	31.1
<65 years	73	68.9
Gender		
Female	11	10.4
Male	95	54
Stage		
Limited	48	89.6
Extensive	52.9	47.1
History of smoking		
Present	65	90.3
ECOG PS* scale		
PS 0-1	68	77.3
PS≥2	20	22.7
Weight loss	31	79.5
LDH**		
Higher	18	36
Hemoglobin***		
Low	22	29.3

*ECOG PS: Eastern Cooperative Oncology Group
**Higher than 1.5 times of normal limit
***Lower than 10g/dl

received a combination therapy of cisplatin and etoposide that was given in a mean of 4 to 6 cycles. After treatment was completed, partial response (PR) or complete response (CR) were achieved in 71.2% of patients with SCLC. 71.7% of patients with LSD were given radiotherapy, but other were not due to medical co-morbidities.

There are no statistically significant relations between prognostic factors like age, sex, LDH level, hemoglobin level, weight loss, PS and OS or PFS by univariate analysis (p>0.5). In addition, multivariate analysis showed that there was no statistically correlation among PS, LDH level, weight loss, sex, age and median survival (p>0.05) also. Median survival time and PFS times were 14.2 and 8 months; 19.7 and 11 months in LSD and 9.1 and 7.2 months in ESD, respectively (Figure 1). Overall survival in 1 and 2 years were 58% and 23% respectively. We detected only the stage of disease as a prognostic factor for OS (p=0.001) and PFS (p=0.003) (Table 2).

DISCUSSION

The most important known cause of SCLC is cigarette smoking, accounting for approximately 95% of cases and is rarely observed in someone who had never smoked [3,9,10]. There was a history of smoking about 90.3% of patients with SCLC analyzed in our study. This result was concordance with the literature. Complete evaluation of patients with SCLC consist of history, physical examination, complete blood count, electrolytes, LDH, urea, creatinine, liver function tests, CT of thorax, abdomen and MRI of brain. Also, evaluation of bone metastasis, radionuclide bone scanning is required [1,8,11].

SCLC is staged according to the Veteran's Administration Lung Cancer study group as LSD or ESD. Patients with LSD have involvement restricted to ipsilateral hemithorax that can be set in one radiotherapy area,

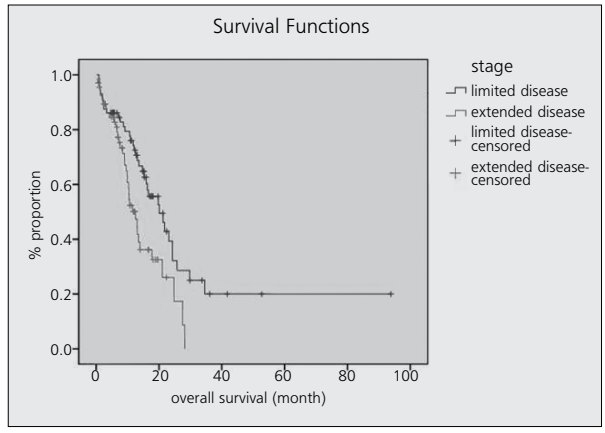

Figure 1. The overall survival curve of patients according to stage

Table 2. The relationship between prognostic factors and median survival and progression free survival according to univariate analysis

Prognostic factors	Median survival time (months)	CI 95%	p	Median PFS time (monhs)	CI 95%	p
Age			0.924			0.9
<65 years	13.9	10.93-16.86		7.43	6.27-8.99	
>65 years	17.73	8.93-26.53		8.16	4.28-12.04	
Overall	14.2	10.82-17.57		8.06	6.83-9.30	
Sex			0.201			0.2
Female	15.26	10.99-19.54		11.03	2.03-20.03	
Male	14.2	9.87-18.52		7.63	6.80-8.46	
Stage			0.001			<0.001
Limited	19.76	13.01-26.52		11.03	5.21-16.84	
Extensive	9.10	5.79-12.40		7.23	6.42-8.03	
Weight loss			0.137			0.2
Present	10.09	6.58-15.21		7.23	6.22-8.23	
LDH level*			0.085			0.8
High	13.03	8.78-17.28		9.1	7.21-10.98	
Hemoglobin level			0.558			0.3
Low**	21.36	3.52-39.20		6.93	7.21-10.98	
PS			0.067			0.9
0-1	16.4	10.06-22.73		8.06	6.42-9.71	
≥2	12.03	7.42-16.64		7.43		

*Higher than 1.5 times of normal limit
**Lower than 10g/dL

presence of ipsilateral supraclavicular lymph nodes and ipsilateral pleural effusions with unknown cytological diagnosis. ESD is defined as the presence of overt metastatic disease by imaging [1-3,12,13]. Malignant pleural effusion or contralateral supraclavicular nodes or contralateral hilar nodes are considered to be ESD [9]. The stage of disease is the most important predictor of improvement and survival in SCLC [5]. As it was known that LSD to ESD ratio was 1/1, while new developments are seen in imaging techniques, this ratio changed to 1/3 [12,14]. In our study, LSD was 52.9% and ESD was 47.1%. Median survival times are 15-20 months for LSD and 20-40% of patients survive 2 years but, for ESD, median survival time is 8-13 months and approximately only 5% of patients survive 2 years [2,9,12]. Torun et al. [13] reported that median survival time for LSD and ESD were 8 months and 3 months, respectively and stage of disease was an important prognostic factor for median survival. We found that median survival time was 14.2 months (SE: 1.7, 95% CI; 10.8-17.5); 19.7 months (SE: 3.4, 95% CI; 13-26.5) in LSD and 9.1 months (SE: 1.6, 95% CI; 5.7-12.4) in ESD, respectively. OS in 1 and 2-years were also 58% and 23%, respectively.

The most important prognostic factors are disease stage, PS, male gender, extent of weight loss and LDH level [3,8,12]. Cancer and Leukemia Group B (CALGB) identified female sex and PS as important predictors of survival both in LSD and ESD. LSD patients older than 60 years had a higher mortality rate than younger patients, but age was not predictive of survival in ESD [15]. Torun et al. [13] reported that stage and PS were major prognostic factors, but there was no relationship between age, alkaline phosphatase level and survival. Although they showed LDH related survival by using univariate analysis, it could not be confirmed by multivariate analysis. In another study, elevated level of LDH in patient with LSD predicted poorer survival relative to those with LDH in normal range. A possible explanation of this relationship may be that, LDH estimates tumor burden in patient with LSD and suggests that LDH identifies occult disease not detected by current staging investigation [6]. Ray et al. [16] documented that weight loss, high LDH level was accepted as prognostic factors for SCLC, but not achieving complete response to treatment. Another study concluded that stage and PS were more predictive than age in the survival of SCLC. Chute et al. [11] documented that male gender, PS<2, and presence of liver metastasis were associated with worse prognosis ESD, and in LSD PS>1, male gender were found to be adverse factors in survival. While we statistically found, by using multivariate analysis, that extensive stage was a prognostic factor associated with worse prognosis but not LDH level, weight loss, age, sex and hemoglobin level in our patients, so only stage of disease had statistically prognostic importance (p=0.001).

Although SCLC is sensitive to chemotherapy, local failure occurred in 50-90% of cases when using chemotherapy as single modality. Addition of radiotherapy to the thorax improves local control and increase survival [9,12,14]. Combined modality treatment with concomitant chemoradiotherapy is the current standard of treatment. Two meta-analysis have shown a 5% improvement in 3-year survival rates for patients receiving a combination of chemotherapy and radiotherapy versus receiving chemotherapy alone [8]. Sequential, alternating, concurrent approaches have been tried in integrating radiotherapy and chemotherapy and in early studies no statistically significant difference was found among them, but the Japanese Clinical Oncology Group (JCOG) study showed improvement in overall survival with concurrent therapy in LSD [8]. When platinum etoposide regimens are used, concurrent radiotherapy is superior to sequential radiotherapy [1]. In our patients, we also used combination chemotherapy and radiotherapy sequentially in LSD but not concomitant due to technical problems related to radiotherapy.

Patients with ESD are treated with palliative chemotherapy, whereas patients with LSD are treated with curative intent to achieve a 5-year survival rate of 20% [8,18]. With standard chemotherapy LSD has a response rate of 80-90% and also a complete clinical response can be achieved in 50-60% of patients. On the other hand, in ESD, chemotherapy is palliative because duration of response is short [9]. Platinum-based chemotherapy remains the mainstay of treatment of both LSD and ESD. Cisplatin and etoposide combination is standard for SCLC and usage of 4 to 6 cycles offer significant survival advantage in patients with SCLC. Randomized studies evaluating the role of maintenance therapy did not relieve any survival advantage for prolonged treatment [8]. The issue of carboplatin versus cisplatin was reviewed in literature who concluded that, carboplatin and etoposide seems to be as effective, but less toxic, than the cisplatin plus etoposide regimen [1,7,8,11]. Because of lower toxicity, the carboplatin included regimen could be preferred for patients with low creatinine clearance and older patients [2,8,12]. We used a rate of 87.8% of cisplatin plus etoposide combination for a median 6 cycles as the first line chemotherapy regimen for patients with SCLC. After the end of treatment, about 71.2% CR plus PR were achieved.

The risk of central nervous metastasis developing 2 years after treatment of SCLC is approximately 35-65%. Thus, prophylactic cranial irradiation (PCR) was introduced for responsive LSD [1,8]. A meta-analysis of efficacy of PCR in 847 patients with LSD and 147 patients with ESD who had complete remission with chemotherapy and radiotherapy demonstrated a 25.3% decrease in incidence of brain metastasis and increase in overall survival of 5.4% in 3 years with PCR [8,9,12]. National Comprehensive Cancer Network recommends PCR for patients with either LSD or ESD who achieve complete response [8]. Only 3 patients could be given prophylactic cranial radiation in our study because of technical problems related to radiotherapy.

CONCLUSION

Although SCLC has a high initial response to chemotherapy and radiotherapy, 5-year survival is still 15% to 25% for patients with LSD and less than <1% for patients with ESD. The median survival time is markedly increased from 2 to 3 months in untreated patients to 8 to 16 months in patients treated with chemotherapy. Therefore it is important to define pretreatment prognostic factors that correlate with extent of disease in order to predict responsivity to treatment and survival following diagnosis.

Conflict of Interest

No conflict of interest was declared by the authors.

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